HHS Public Access

Author manuscript

Pharmacol Biochem Behav. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Pharmacol Biochem Behav. 2016 February ; 141: 66–77. doi:10.1016/j.pbb.2015.12.002.

Adolescent methylphenidate treatment differentially alters adult impulsivity and hyperactivity in the Spontaneously Hypertensive Rat model of ADHD

S.S. Somkuwar[a], **K.M. Kantak**[b], **M.T. Bardo**[c], and **L.P. Dwoskin**[a]

[a]Department of Pharmaceutical Sciences, University of Kentucky, Lexington, Kentucky 40536, USA

[b]Department of Psychological and Brain Sciences, Boston University, Boston, Massachusetts 02215, USA

[c]Department of Psychology, University of Kentucky, Lexington, Kentucky 40536, USA

Abstract

Impulsivity and hyperactivity are two facets of attention deficit/hyperactivity disorder (ADHD). Impulsivity is expressed as reduced response inhibition capacity, an executive control mechanism that prevents premature execution of an intermittently reinforced behavior. During methylphenidate treatment, impulsivity and hyperactivity are decreased in adolescents with ADHD, but there is little information concerning levels of impulsivity and hyperactivity in adulthood after adolescent methylphenidate treatment is discontinued. The current study evaluated impulsivity, hyperactivity as well as cocaine sensitization during adulthood after adolescent methylphenidate treatment was discontinued in the Spontaneously Hypertensive Rat (SHR) model of ADHD. Treatments consisted of oral methylphenidate (1.5 mg/kg) or water vehicle provided Monday-Friday from postnatal day 28–55. During adulthood, impulsivity was measured in SHR and control strains (Wistar Kyoto and Wistar rats) using differential reinforcement of low rate (DRL) schedules. Locomotor activity and cocaine sensitization were measured using the open-field assay. Adult SHR exhibited decreased efficiency of reinforcement under the DRL30 schedule and greater levels of locomotor activity and cocaine sensitization compared to control strains. Compared to vehicle, methylphenidate treatment during adolescence reduced hyperactivity in adult SHR, maintained the lower efficiency of reinforcement, and increased burst responding under DRL30. Cocaine sensitization was not altered following adolescent methylphenidate in adult SHR. In conclusion, adolescent treatment with methylphenidate followed by discontinuation in adulthood had a positive benefit by reducing hyperactivity in adult SHR rats; however,

Corresponding Author: Linda P. Dwoskin, Ph.D., Address: 789 South Limestone, 465 Biological Pharmaceutical Complex, Lexington, KY 40536 Phone: (859) 257-4743, Fax: (859) 257-7585, ldwoskin@email.uky.edu.

CONFLICT OF INTEREST

The authors have no financial interests or conflicts of interest to disclose.

increased burst responding under DRL compared to SHR given vehicle, i.e., elevated impulsivity, constituting an adverse consequence associated with increased risk for cocaine abuse liability.

Keywords

Attention Deficit/Hyperactivity Disorder; Impulsivity; Differential Reinforcement of Low Rates Schedule; Methylphenidate; Spontaneously Hypertensive Rat

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD), a neurobehavioral disorder affecting 12% of children and 5% of adults (Biederman, Petty et al. 2010), is characterized by increased impulsivity, hyperactivity and inattention (Bearden, Reus et al. 2004, Castellanos, Sonuga-Barke et al. 2005, American Psychiatric Association. 2013). Impulsivity, a broad psychological construct, encompasses a variety of maladaptive behaviors, e.g., actions that are poorly conceived, unnecessarily risky and prematurely executed without sufficient forethought (Evenden 1999). Response inhibition capacity, an endophenotype of impulsivity (Almasy and Blangero 2001, Gottesman and Gould 2003, Slaats-Willemse, Swaab-Barneveld et al. 2003, Crosbie, Perusse et al. 2008), is an executive control mechanism preventing premature execution of intermittently reinforced actions (Barkley 1997, Aron 2007). Deficits in response inhibition are reported in ADHD (Clark, Blackwell et al. 2007, Crosbie, Perusse et al. 2008).

Methylphenidate (MPH), the most widely prescribed pharmacotherapy for ADHD (Goldman, Genel et al. 1998, Robison, Sclar et al. 1999, CDC 2007), increases response inhibition capacity in children and adolescents with ADHD (Rhodes, Coghill et al. 2006, Coghill, Rhodes et al. 2007). Therapeutic effects of MPH are due, in part, to increased extracellular dopamine (DA) in prefrontal cortex (Berridge, Devilbiss et al. 2006, Berridge and Devilbiss 2011). Adolescence represents a vulnerable period for cortical neuronal development, and during this period, MPH treatment may alter the normal developmental trajectory of the prefrontal cortex (Chambers, Taylor et al. 2003, Casey and Jones 2010, Counotte, Smit et al. 2011). Regarding long-term consequences, studies in outbred rats show that low doses of MPH during adolescence decrease impulsive choice during adulthood, such that delayed larger rewards are chosen over immediate smaller rewards (Adriani, Canese et al. 2007). Other beneficial long-term consequences of MPH treatment in outbred adolescent rats include the absence of an increase in the psychomotor response to cocaine (Brandon, Marinelli et al. 2001) and increases in prefrontal cortical neuron excitability and phosphocreatine/creatine ratios, indicating increased energy utilization during adulthood (Adriani, Canese et al. 2007, Urban, Waterhouse et al. 2012, Urban, Li et al. 2013). However, outbred rats do not adequately model deficits in ADHD, such as increased impulsivity, inattention and enhanced sensitivity to reinforcement delays (Russell, de Villiers et al. 1995, Sagvolden, Aase et al. 1998, Sagvolden, Russell et al. 2005). Thus, MPH given during adolescence may produce different outcomes in rats exhibiting an ADHD phenotype.

The Spontaneously Hypertensive Rat (SHR), the most widely accepted model of ADHD, displays many phenotypic characteristics of ADHD, including impulsivity (Adriani, Caprioli et al. 2003, Mill, Sagvolden et al. 2005, Sagvolden, Russell et al. 2005, Sanabria and Killeen 2008). Wistar-Kyoto (WKY), an inbred progenitor strain from which SHR are derived, and Wistar (WIS), an outbred strain and common ancestor of SHR and WKY, are controls for SHR. Of note, WKY from Charles River/GER, a model for the predominantly inattentive subtype of ADHD (Sagvolden, Dasbanerjee et al. 2008), have a large number (35%) of discordant SNP genotypes relative to WKY from Harlan/UK, a well-recognized control for SHR (Sagvolden, Johansen et al. 2009). In contrast, WKY from Charles River/US have a small number (2.5%) of discordant SNP genotypes relative to WKY from Harlan/UK (Zhang-James, Middleton et al. 2013), and are not expected to differ from WKY from Harlan/UK. Thus, WKY from Charles River/US were used as the inbred control herein. Outbred controls (e.g., WIS) were also used, as they help to disambiguate differences between SHR and WKY, and control for the hyper-responsiveness to acute stress exhibited by WKY from Charles River and Harlan (Pare and Kluczynski 1997, De La Garza and Mahoney 2004, Alsop 2007, Langen and Dost 2011).

In SHR, chronic oral MPH at therapeutically relevant doses improves cognitive deficits (Kantak, Singh et al. 2008, Harvey, Jordan et al. 2013). However, chronic MPH administered to adolescent SHR also produces maladaptive sequelae, including increased anxiety and cross-sensitization to cocaine (Vendruscolo, Izidio et al. 2008, Yetnikoff and Arvanitogiannis 2013). Moreover, chronic MPH treatment during adolescence, followed by treatment discontinuation, increases cocaine self-administration in adult SHR compared to SHR receiving vehicle and compared to WKY and WIS given MPH or vehicle (Harvey, Sen et al. 2011). In contrast, WIS treated with MPH show reduced acquisition of cocaine self-administration compared to vehicle control during adulthood (Harvey, Sen et al. 2011), consistent with previous reports using outbred rats (Carlezon, Mague et al. 2003, Thanos, Michaelides et al. 2007). Further, chronic MPH in adolescent SHR decreases markers of neuronal plasticity in adolescent prefrontal cortex (Fumagalli, Cattaneo et al. 2010), suggesting that the prefrontal cortex may be critical in modulating the long-term consequences of MPH treatment during adolescence. Chronic MPH during adolescence increases DA transporter (DAT) function in SHR medial prefrontal cortex (mPFC) (Somkuwar, Darna et al. 2013), suggesting decreased extracellular DA during adulthood, long after discontinuation of MPH treatment. Decreased mPFC DA is associated with increased responsiveness to cocaine and increased response inhibition deficits in a differential reinforcement of low rate (DRL) 30 s schedule (Schenk, Horger et al. 1991, Sokolowski and Salamone 1994). Although not empirically determined, these previous findings suggest that chronic MPH treatment during adolescence leads to increased deficits in response inhibition capacity and increased cocaine sensitivity during adulthood, specifically in SHR.

The current study used DRL schedules in SHR to evaluate effects of MPH treatment during adolescence on response inhibition capacity during adulthood. Under a DRL schedule, subjects must wait for a defined time period between consecutive responses to earn a reinforcer, i.e., inter-response times (IRT) greater than an experimenter-defined minimum interval are reinforced (Monterosso and Ainslie 1999). Deficits in response inhibition

capacity (or premature responding) are inferred from the reduced efficiency of earning reinforcers (Stein and Landis 1975). Increased reinforcement density reduces behavioral deficits in individuals with ADHD and in SHR (Wultz and Sagvolden 1992; Aase and Sagvolden 2006). Compared to WIS, deficits in SHR are reported under relatively difficult tasks in strategy set-shifting schedules (Harvey, Jordan et al. 2013). Thus, DRL 5 s limited hold (DRL5LH) and DRL 30 s (DRL30) with a high and low reinforcement density, respectively, evaluated response inhibition capacity herein. Short DRL schedules, including DRL30, are sensitive to effects of ADHD medications (Peterson, Wolf et al. 2003, Hankosky and Gulley 2013). Compared to WKY and several outbred strains, adult SHR exhibit reduced efficiency under DRL schedules (Bull, Reavill et al. 2000, van den Bergh, Bloemarts et al. 2006, Ferguson, Paule et al. 2007, Sanabria and Killeen 2008, Orduna, Valencia-Torres et al. 2009). In the present study, a novel modeling approach was used to analyze the microstructure of DRL responding. Further, cocaine-induced hyperactivity and cocaine sensitization were measured in adult SHR, WKY and WIS to determine the long-term consequences of adolescent MPH on cocaine-related behaviors other than self-administration examined previously.

2 Methods

2.1 Subjects

Male SHR and WKY (Charles River Laboratories, Kingston, NY) and male WIS (Charles River Laboratories, Raleigh, NC) rats (postnatal day 25 [P25] upon arrival) were maintained on a 12-h light:dark cycle (on 07:00 h), and housed individually with free access to food and water. After 3 habituation days, rats were food-restricted to 90–95% of expected free-feeding body weight. Group size (n=6/group) was based on previous studies using a quantitative modeling approach to evaluate behavior under DRL schedules (Sanabria and Killeen 2008, Hill, Covarrubias et al. 2012). The sequence of experiments, conducted during the light phase, is presented in Fig 1. Principles of laboratory animal care were followed; protocols were conducted according to the 2012 *National Institutes of Health Guide for the Care and Use of Laboratory Animals* and approved by the University of Kentucky Institutional Animal Care and Use Committee.

2.2 Drugs and treatments

(±)-Methylphenidate HCl (MPH; Sigma-Aldrich, St Louis, MO) dissolved in 1.5 mg/ml water was injected into oyster crackers for oral (p.o.) dosing (Kantak, Singh et al. 2008). Crackers injected with water (1 ml/kg) served as vehicle control. Cocaine HCl, a gift from the National Institute on Drug Abuse (Bethesda, MD, USA), was dissolved in sterile saline (0.9% w/v) at 10 mg/ml and injected at 10 mg/kg (i.p.) to determine acute locomotor activation and induction of sensitization. For expression of sensitization, cocaine solutions (5, 7.5 and 15 mg/ml) were prepared for doses ranging from 5–15 mg/kg (i.p.). Solutions were prepared fresh each day.

2.3 Methylphenidate treatment during adolescence

SHR, WKY and WIS were treated with MPH (1.5 mg/kg, p.o.) or vehicle from P28 to P55, early to late adolescence (Spear 2000, Doremus-Fitzwater, Varlinskaya et al. 2010). Given

inherent species differences in MPH absorption, distribution, metabolism and elimination, complete agreement has not been reached on the ideal method for arriving at clinically-relevant MPH doses for preclinical studies. For the current series of experiments, a 1.5 mg/kg dose of MPH was chosen as it produces therapeutically relevant plasma concentrations (9–36 ng/ml plasma) in rats (Wargin, Patrick et al. 1983, Kuczenski and Segal 2002), enhances extracellular DA and NE in the prefrontal cortex to improve cognitive function (Berridge, Devilbiss et al. 2006), and is below the threshold for producing hyperactivity (Gerasimov, Franceschi et al. 2000, Kuczenski and Segal 2002). This chronic regimen of MPH treatment improved working memory and visual discrimination learning in adolescent and adult SHR, but not in WKY and WIS (Kantak, Singh et al. 2008, Harvey, Sen et al. 2011). Doses were given Monday to Friday modeling weekend "medication holidays" in patients with ADHD (Martins, Tramontina et al. 2004). After P55, rats were maintained in their home cages with *ad libitum* access to food and water.

2.4 Differential reinforcement of low-rate schedules

Effects of MPH during adolescence on impulsivity in adulthood were determined using a DRL schedule in operant conditioning chambers (Supplementary Methods). Starting at P77, rats were food restricted to 90–95% of expected free-feeding body weight and trained in daily 55-min sessions under DRL5secLH, and subsequently in DRL30sec, as described previously (Sanabria and Killeen 2008); detailed in Supplementary Methods). For DRL30, LH was not employed because long IRTs are infrequent under DRL schedules with low reinforcement density (Richards, Sabol et al. 1993, Sanabria and Killeen 2008); Supplementary Results). Number of active and inactive lever responses, pellets earned, and IRTs were recorded over 5 sessions of stable performance. Response efficiency under DRL30 in SHR was ~6% (Supplementary Results), such that longer waiting times associated with longer DRLs may have resulted in a floor effect in response efficiency. Following completion of the DRL study, rats were maintained in the home cage with ad libitum access to food and water.

2.5 Open-field activity

Effect of MPH during adolescence on locomotor activity in adult rats was determined 3–5 days after DRL study completion. SHR, WKY and WIS rats were habituated for 3 days during 1-hr sessions in acrylic open-field chambers (42 × 42 × 30 cm), each with a 16 × 16 photobeam sensor grid and a monitoring system (AccuScan Instruments Inc., Columbus, OH). Activity was recorded during the 3 habituation days as horizontal beam breaks and repeated breaks to capture both gross and fine movements respectively..

2.5.1 Acute cocaine-induced hyperactivity—One day after the open-field activity assay, cocaine-induced hyperactivity was determined in the same open-field chambers. On consecutive days, rats were injected acutely with cocaine (10 mg/kg, i.p.) and saline (1 ml/kg, i.p.) in a random order. Activity was recorded for 1 hr. Rats were not habituated to the injection procedure.

2.5.2 Sensitization to repeated cocaine administration—Following determination of acute cocaine-induced hyperactivity, all rats were administered cocaine (10 mg/kg, i.p.,

once daily for 10 days), placed in the chambers for 1 hr and activity recorded. Strain differences and effects of adolescent MPH treatment on induction of cocaine sensitization were determined. Upon completion of the 10-day repeated treatment phase, rats remained undisturbed in the home cage for a 14-day cocaine-free period without access to the chambers. On the 15th day, expression of cocaine sensitization was determined by injecting cocaine (0, 5, 7.5 and 15 mg/kg, i.p., ascending dose order within a single 2-hr session); activity was monitored for 30 min after each dose. Note that the control was a volume matched saline injection and hence, is referred to saline in the corresponding results and figures for this experiment.

2.6 Data analysis

2.6.1 Modified temporal regulation (TR) model—Therapeutically relevant, acute doses of MPH do not alter efficiency of reinforcement under DRL (van den Bergh, Bloemarts et al. 2006, Ferguson, Paule et al. 2007, Orduna, Valencia-Torres et al. 2009). However, for evaluating MPH effects on response inhibition capacity under DRL, quantitative TR modeling of IRT-distribution patterns is more sensitive than is efficiency (Sanabria and Killeen 2008, Hill, Covarrubias et al. 2012). Modified TR models, quantifying IRT distributions obtained under DRL5LH and DRL30, are defined by Equations 1 and 2, respectively (Supplementary Methods; Fig S1). Both models segregate IRT distributions between timed IRTs expected to congregate near the target time (e.g., 5 s for DRL5LH, and 30 s for DRL30), and non-timed, exponentially distributed IRTs (Sanabria and Killeen 2008, Hill, Covarrubias et al. 2012, Mika, Mazur et al. 2012).$P(IRT = t) = p\Gamma(t - \delta; N, c) + q(1 - p)Le^{-L(t-\delta)} + (1 - q)(1 - p)L'e^{-L'(t-\delta)}$ (EQ 1 for DRL5LH); $P(IRT = t) = p\Gamma(t - \delta; N, c) + (1 - p)\lambda e^{-\lambda(t-\delta)}$; $0 < \delta < t$ (EQ 2 for DRL30). Parameters from mathematical models serve as dependent variables describing response inhibition capacity: (1) Response threshold $\theta = (Nxc)/5$ s and $(Nxc)/30$ s for DRL5LH and DRL30, respectively, where (Nxc) is the mean of timed IRTs. $\theta < 1$ indicates reduced accuracy of timed IRTs. (2) Proportion of timed IRTs (p) is expressed as a fraction of all IRTs obtained from an individual rat. A large value for p indicates greater response inhibition capacity. (3) Proportion of burst IRTs ($q*(1-p)$) and ($1-p$) for DRL5LH and DRL30, respectively, is expressed as a fraction of all IRTs obtained from an individual rat. Burst IRTs are a component of non-timed IRTs. A greater proportion of burst IRTs indicates reduced response inhibition capacity. The model also provides $1/L$ and $1/\lambda$, which are the mean burst IRTs for DRL5LH and DRL30, respectively, and the Weber-fraction (ω), an index of the precision of timing. Fraction m ($(1-p)*(1-q)$) and rate-of-decay (L') of long IRTs under DRL5LH characterize task-delinquent responses (McClure and McMillan 1997).

One WKY died prior to treatment initiation and data collection. All data were analyzed using SPSS Statistics Version 19 (SPSS Inc., IBM Company, Armonk, NY). Efficiency of reinforcement (% responses reinforced) and modeling dependent variables for response inhibition capacity were compared between groups. Data are reported as mean ± S.E.M.; n represents number of rats/group. For evaluating MPH effects, 2-factor ANOVA (strain X treatment) were followed by Bonferroni's test corrected for multiple comparisons. Main effects of strain and treatment were evaluated using Tukey's tests. Significance was assessed at $\alpha = 0.05$. Under DRL30, proportion of burst IRTs emitted by one WKY given vehicle was

excluded as the value was identified as an outlier using the Grubbs test (GraphPad; http://www.graphpad.com/quickcalcs/Grubbs1.cfm).

2.6.2 Open-field activity and cocaine sensitivity—Mean ± S.E.M. of total number of horizontal beam breaks, repeated breaks of the same beam, as well as percent time spent in the margins during 1-hr sessions of open-field activity (i.e., the last day of habituation), are presented. Temporal changes in open-field activity (last day of habituation) are reported as mean ± S.E.M. of horizontal beam breaks for every 5-min bin during the 1-hr session. For cocaine hyperactivity, total number of beam breaks and repeated breaks of the same beam are reported as mean ± S.E.M. during the 1-hr sessions following saline and cocaine injections. For induction of sensitization, total number of horizontal beam breaks are reported as mean ± S.E.M. during the daily 1-hr sessions. For expression of sensitization, mean ± S.E.M. for total number of beam breaks and number of repeated breaks of the same beam during the 30-min period after each cocaine dose are reported. Dependent measures for open-field activity were analyzed using 2-factor ANOVA with adolescent treatment (2 levels) and strain (3 levels) as between-subject factors. Furthermore, temporal changes in open-field activity were evaluated using repeated measures 2-factor ANOVA with adolescent treatment and strain combination (6 levels) as between-subject factors and time (12 levels) as a within-subject factor. Cocaine hyperactivity and expression of sensitization were analyzed using repeated-measures 3-factor ANOVAs with cocaine dose as a within-subject factor for hyperactivity (2 levels) and for expression of sensitization (4 levels). Mauchly's tests of Sphericity tested the assumption of sphericity of variance for repeated-measures ANOVAs. When sphericity was violated, Greenhouse-Geisser correction determined within-subject effects. Main effects and interactions were evaluated using Bonferroni's *post-hoc* analyses corrected for multiple comparisons. For evaluating induction of sensitization, a 3-way repeated-measures ANOVA was conducted. Session (10 levels) served as a discreet within-subject variable and adolescent treatment (2 levels) and strain (3 levels) as between-subject variables. Linear mixed model analyses have been shown to be more powerful statistical analyses compared to traditional repeated measures ANOVA, particularly, for data with large number of observations (Wainwright, Leatherdale et al. 2007, Baayen, Davidson et al. 2008). Therefore, a complementary linear mixed model analysis was conducted (Verbeke and Molenberghs 2000) for induction of sensitization using session (10 levels) as a within-subject continuous variable and adolescent treatment (2 levels) and strain (3 levels) as between-subject variables. Session x strain and session x treatment interactions were probed further using linear regression analyses to identify differences in rate of change of locomotor activity with repeated cocaine injections.

3 Results

3.1 Response inhibition capacity

Rats reached stability in DRL5LH within 12–16 sessions; IRT distribution patterns are presented for adult SHR, WKY and WIS administered MPH or vehicle during adolescence (Fig 2). MPH during adolescence in SHR did not alter percent of responses reinforced (efficiency; Table 1), proportions of timed IRTs and burst IRTs as well as mean timed IRTs (Supplementary Results, Fig S2), indicating no effect on impulsivity under DRL5LH in the

ADHD model. Strain differences were identified, such that percent of responses reinforced (i.e., efficiency) was lower in SHR compared to WIS and WKY (Table 1), indicating greater impulsivity in SHR compared to control. Surprisingly, WKY administered vehicle emitted a lower proportion of timed IRTs compared to WIS, and MPH treatment during adolescence normalized this measure of impulsivity in WKY (*p*; $F_{interaction}[2, 29] = 5.19$, $p < 0.05$; Supplementary Fig S2A).

Under DRL30, rats required 17–22 sessions to reach stability; mean IRT distribution patterns are presented for SHR, WKY and WIS administered MPH or vehicle during adolescence (Fig 3A). A main effect of strain was found for efficiency ($F_{strain}[2,29] = 32.9$, $p<0.05$; Table 1), with SHR < WKY and WIS, suggesting greater impulsivity in SHR; main effect of treatment and the strain x treatment interaction were not significant. A main effect of strain for accuracy of timed IRTs was found (θ; $F_{strain}[2,29] = 32.9$, $p<0.0001$; Fig 3B), with SHR<WIS<WKY; main effect of treatment and the strain x treatment interaction were not significant. Moreover, a strain x treatment interaction was found for proportion of burst IRTs emitted ($(1-p)$; $F_{interaction}[2,28] = 3.58$, $p<0.05$; Fig 3C), with SHR > WKY and WIS after vehicle. Importantly, adolescent MPH further increased burst IRTs only in SHR during adulthood ($p<0.05$). Thus, adult SHR were more impulsive than control WKY and WIS, and adolescent MPH further increased impulsivity in adult SHR, as indicated by an increased proportion of burst IRTs under DRL30.

3.2 Open-field activity

At baseline, adult SHR exhibited a greater number of total horizontal beam breaks compared to WKY, but SHR were not different from WIS; WKY exhibited a lower number of total beam breaks compared to WIS ($F_{strain}[2, 29] = 40.4$, $p<0.0001$; Fig 4A). Thus, at baseline, WKY were hypoactive relative to both SHR and WIS; and importantly, SHR were not hyperactive relative to WIS. Total horizontal beam breaks during adulthood were decreased following adolescent MPH treatment in all strains ($F_{treatment}[1, 29] = 12.3$, $p<0.01$; Fig 4A); no strain x treatment interaction was found. With the temporal change of activity analysis, number of beam breaks decreased with time in all strains irrespective of treatment history ($F_{time}[11, 319] = 71.1$, $p<0.0001$; Fig 4B). During the first two 5-min bins, SHR made greater beam breaks compared to WKY, and WKY made fewer beam breaks compared to WIS ($F_{strain\text{-}treatment\ combination}[5, 319] = 12.3$, $p<0.0001$). Importantly, during the first 5 minutes of open-field access, SHR with a MPH history, but not with a VEH-treatment history, exhibited reduced horizontal beam breaks compared to WIS that received vehicle during adolescence ($F_{interaction}[55,319] = 1.50$, $p<0.05$; Fig 4B). Thus, MPH treatment during adolescence decreased hyperactivity in adult SHR.

Further evaluation of open-field activity revealed that SHR produced a greater number of repeated breaks of the same beam compared to both WKY and WIS ($F_{strain}[2, 29] = 21.4$, $p<0.0001$; Fig 4C). MPH treatment during adolescence reduced the number of repeated breaks of the same beam in all adult strains ($F_{treatment}[1, 29] = 5.54$, $p<0.05$; Fig 4C); no strain x treatment interaction was found. Furthermore, adult WKY rats, but not SHRs, were found to spend significantly greater time near the margins of the open-field chamber

compared to WIS (F_{strain}[2, 29] = 15.0, p<0.0001; Fig 4D); SHR were not different from WIS. No effects of MPH treatment or strain x treatment interaction were found.

3.3 Cocaine sensitivity

Acute cocaine-induced hyperactivity—Compared to saline, acute cocaine produced total horizontal beam breaks in all strains ($F_{cocaine}$[1,32] = 14.6, p<0.001; Fig 5); no interactions were found. A main effect of strain on activity was found, with SHR and WIS > WKY (F_{strain}[2, 32] = 21.2; p<0.01), but SHR did not differ from WIS.

SHR exhibited a greater number of repeated breaks of the same beam compared to WKY, but not compared to WIS (F_{strain}[2, 32] = 11.87; p<0.0001; Supplementary Fig S3). No effects of cocaine or MPH treatment history or interaction were revealed.

Induction of cocaine sensitization—A strain x session interaction ($F_{strain\ X\ session}$[18,56.3] = 6.21; p<0.01), but no interaction of treatment x session or strain x treatment x session, were found using the Linear Mixed Model analysis, indicating that induction of sensitization differed between strains, but not between treatment groups (Fig 6A–C). Data for sensitization induction were collapsed across treatment (Fig 6D). Further evaluation of the strain x session interaction revealed cocaine sensitization was greater in SHR (F[2,344] = 11.9, p<0.0001; the rate of change in photobeam-breaks/session = 1390 ± 185) compared to WKY and WIS (the rate of change in photobeam-breaks/session = 337 ± 132 and 445 ± 193, respectively). Using repeated measures ANOVA, treatment x strain x session and the treatment x session interactions were not significant. However, the strain x session interaction (F[18,261] = 3.21, p<0.001) and the main effect of session (F[9,261] = 14.4, p<0.001) were significant, which was consistent with the Linear Mixed Model analysis. MPH treatment during adolescence did not alter the induction of sensitization to repeated cocaine in adult rats. Therefore, sensitization data were collapsed between adolescent vehicle and MPH groups. The strain x session interaction was evaluated using separate repeated-measures two-way ANOVAs, followed by Dunnett's post-hoc comparisons of the 2nd through 10th sessions to the 1st session of cocaine administration for individual strains and followed by Tukey's test to compare between-strain differences (Fig 6E). For SHR, activity was elevated (F[9,99] = 15.2, p<0.0001) from the 4th to the 10th session compared to the 1st session of repeated cocaine (ps<0.05). For WKY, activity differed by session (F[9,90] = 3.64, p<0.001), but Dunnett's post-hoc analysis did not reveal significant pairwise differences compared to the 1st day of repeated cocaine. For WIS, activity was not elevated by repeated cocaine injection (F[9,99] = 1.92, p>0.05). Across strains, activity in SHR was greater than WKY from the 3rd session to the 10th session, and was greater than WIS from the 6th to the 10th session (ps<0.05). Activity in WKY was lower than WIS on the 4th, 8th and 10th sessions (ps<0.05). Overall, these results suggest that sensitization did not differ with prior MPH treatment, but was differentially induced in SHR vs. the WKY and WIS control strains.

Expression of cocaine sensitization—With respect to total horizontal beam breaks, a strain x cocaine-dose interaction ($F_{strain\ X\ cocaine}$[6,87] = 7.12, p<0.05) and main effect of cocaine dose ($F_{cocaine}$[3,87] = 28.4, p<0.001) were found; no treatment x strain x cocaine-

dose or treatment x cocaine-dose interactions were found (Fig 7). In SHR, cocaine dose-dependently increased activity; only the highest dose was different from saline (ps<0.05). In contrast, WKY activity was greater with cocaine 7.5 and 15 mg/kg compared to saline, and greater with cocaine 15 mg/kg compared to cocaine 5 mg/kg (ps<0.05). For WIS, 15 mg/kg produced greater activity than 5 mg/kg, but not saline (p<0.05). Thus, dose-related effects of cocaine on sensitization were found for all strains. Following saline injection, activity was greater in SHR and WIS compared to WKY (ps<0.05). Following cocaine injections (5–15 mg/kg), activity was greater in SHR compared to both WKY and WIS (ps<0.05), and the control strains were not different from each other. With regard to the number of repeated breaks of the same beam, a strain x cocaine-dose interaction ($F_{strain\ X\ cocaine}[6,96] = 4.88$, $p<0.001$), the main effect of cocaine dose ($F_{cocaine}[3,96] = 27.0$, $p<0.0001$) and a main effect of strain were found ($F_{strain}[2,32] = 21.8$, $p<0.0001$); treatment x strain x cocaine-dose or treatment x cocaine-dose interactions were not found (Fig 8). SHR exhibited a greater number of repeated beam breaks compared to both WKY and WIS (ps<0.001). In SHR, cocaine dose-dependently increased the number of repeated beam breaks with the highest dose being different from saline, 5 mg/kg and 7.5 mg/kg doses (ps<0.05). In contrast, repeated beam breaks by WKY were greater with cocaine 7.5 mg/kg and 15 mg/kg compared to saline, and greater with cocaine 15 mg/kg compared to cocaine 5 mg/kg (ps<0.05). For WIS, 15 mg/kg produced a greater number of repeated beam breaks than 5 mg/kg, but not compared to saline (p<0.05). Following saline injection, repeated beam breaks were greater in SHR and WIS compared to WKY (ps<0.05). Following cocaine injections (5, 7.5 and 15 mg/kg), number of repeated beam breaks was greater in SHR compared to both WKY and WIS (ps<0.05), and the control strains were not different from each other. Thus, dose-related effects of cocaine on sensitization were found for all strains, and SHR expressed a greater magnitude of cocaine-induced locomotor activity compared to both WKY and WIS.

4 Discussion

To the extent that SHR models ADHD, the current study increases our understanding of the long-term consequences of adolescent MPH treatment. ADHD symptoms often decrease in severity with age, leading to treatment discontinuation in early adulthood (Mannuzza, Klein et al. 1998, Faraone, Biederman et al. 2006, McCarthy, Asherson et al. 2009). Consistent with clinical observations, the current study shows that SHR treated chronically with MPH during adolescence exhibited decreased hyperactivity during adulthood, observed as a decreased total number of beam breaks, particularly during the initial access to the open-field chambers. These results extend previous reports showing that hyperactivity in adolescent outbred Sprague-Dawley rats and adolescent SHR was reduced during acute and sub-chronic MPH treatment during adolescence (Kuczenski and Segal 2002, Umehara, Ago et al. 2013, Umehara, Ago et al. 2013). Furthermore, adolescent MPH treatment was found to decrease other aspects of SHR hyperactivity, specifically stereotypic behavior inferred from repeated breaks of the same photobeam in the open-field chambers. Importantly, the effects of MPH treatment history was not generalized to all types of open field behavior as evidenced by the amount of time spent near the margins as opposed to the center of the box, which is an indication of stress/anxiety. With respect to increased locomotor activity in SHR

relative to WKY, a study evaluating monoamine transporter inhibitors (i.e., selective NET inhibitors: desipramine, reboxetine and atomoxetine; selective SERT inhibitor: citalopram) revealed that inhibitor-induced decreases in hyperactivity in SHR are associated with increased extracellular DA and NE, but not 5-HT in mPFC microdiaysate (Umehara, Ago et al. 2013). In WKY, increased immobility (depression-like behavior) in a forced-swim paradigm, relative to WIS controls, was associated with increased hippocampal NE, 5-HT and glutamate, and importantly, increased NE and 5-HT in frontal cortex (Jastrzebska, Frankowska et al. 2015). Collectively, these findings suggest that functional alterations in several neurotransmitters in prefrontal cortex and other brain regions may underlie the hyperactivity and response to stress in SHR relative to control strains. Thus, hyperactivity in the SHR may be due to elevated DA and NE relative to the control strains, and MPH treatment during adolescence may have normalized the hyperactivity in SHR by producing lasting adaptations in DA and NE in prefrontal cortex.

In the SHR, the MPH treatment regimen maintained the low response efficiency under both DRL schedules herein. While response efficiency is an accepted index of impulsivity, it was ~2.5% in SHR compared to 30% and 10% in WKY and WIS, respectively, suggesting a floor effect for SHR under DRL30. When only response efficiency is considered, a comprehensive understanding of DRL30 behavior is not obtained (Richards, Sabol et al. 1993), as efficiency does not differentiate between errors due to response inhibition and timing. Mathematical modeling of the IRT data employing theoretically based measures of response inhibition capacity more accurately describes DRL behavior (Sanabria and Killeen 2008, Hill, Covarrubias et al. 2012). In the current study, SHR exhibited reduced response inhibition capacity (increased burst IRTs and reduced accuracy under DRL30). Moreover, the more comprehensive evaluation of SHR responding under DRL revealed an important effect of MPH treatment and discontinuation, the exacerbation of response inhibition deficits (increased burst/decreased timed IRTs), which was not apparent when measuring response efficiency. Thus, while discontinuation of adolescent MPH treatment produced a long-term reduction in hyperactivity in adult SHR, an unanticipated adverse consequence was an enhancement of impulsivity.

Impulsivity, including response inhibition deficits under DRL, is associated with decreased DA function in prefrontal cortex of adult outbred rats (Sokolowski and Salamone 1994, Peterson, Wolf et al. 2003, Antonelli, Ko et al. 2013, Pardey, Kumar et al. 2013, Simon, Beas et al. 2013). Both DAT and NET clear extracellular DA in prefrontal cortex (Moron, Brockington et al. 2002, Berridge, Devilbiss et al. 2006). In adult SHR, NET function in orbitofrontal cortex (OFC; a subregion of the prefrontal cortex) is increased compared to WKY and WIS (Somkuwar, Kantak et al. 2015). Also, MPH treatment during adolescence normalized NET function in adult SHR. Thus, elevated NET function in the absence of MPH treatment may contribute to decreased extracellular DA and/or decreased DA receptor signaling in OFC. Reduction in DA receptor availability in the OFC was negatively correlated with response inhibition capacity in humans (Albrecht, Kareken et al. 2014). Inhibition of NET by local infusion of atomoxetine into OFC improved response inhibition capacity in rats (Bari, Mar et al. 2011). These results suggest that increased NET function may underlie, at least in part, the increase in impulsivity in SHR compared to controls. However, impulsivity was not normalized with MPH treatment during adolescence,

suggesting that alternate mechanisms (e.g., serotonin function) may be responsible for the MPH-mediated increase in impulsivity in adult SHRs reported herein.

Serotonergic neurotransmission has been implicated in the control of impulsive behavior (Pattij and Vanderschuren 2008). In mPFC, 5-HT release positively correlated with premature responding on a 1-choice serial reaction time task in outbred Lister-hooded rats (Dalley, Theobald et al. 2002). Using DRL schedules with relatively long wait-times similar to those employed herein, 5-HT2A receptor antagonists increased efficiency in outbred Sprague-Dawley rats, whereas 5-HT1B receptor knockout mice exhibited decreased efficiency (Pattij, Broersen et al. 2003, Anastasio, Stoffel et al. 2011). 5-HT release from cortical slices taken during both adolescence and adulthood did not differ between SHR, WKY and WIS rats (Schlicker, Classen et al. 1988). Moreover, discontinuation of adolescent MPH treatment (2 mg/kg/day, i.p.; either PND 25–39 or PND 50–64) did not result in long term alterations in striatal 5-HT transporter density in adult SHR and WKY (Roessner, Manzke et al. 2009). Thus, 5-HT does not appear to play a critical role in strain differences with respect to impulsivity. However, it is possible that alterations in 5-HT function specifically in prefrontal cortex may be involved in the increased impulsivity (burst-responses in DRL30) observed following discontinuation of MPH treatment (current study).

Age-dependent decreases in impulsivity are associated with developmental maturation of prefrontal cortical DA systems in rats and humans (Brenhouse, Sonntag et al. 2008, Burton and Fletcher 2012, Rothmond, Weickert et al. 2012). In SHR, MPH during adolescence increases mPFC DAT function in adults relative to vehicle control (Somkuwar, Darna et al. 2013). Faster mPFC DA clearance is expected to reduce DA transmission, consistent with increased impulsivity (increased burst responding and decreased efficiency) under DRL30 (Sokolowski and Salamone 1994). MPH during adolescence did not alter mPFC DAT function or increase impulsivity in WKY and WIS controls (Somkuwar et al. 2013; current study). Thus, an underlying mechanism mediating increased response inhibition deficits in SHR given MPH during adolescence likely involves the mPFC DA system.

Acute cocaine produces hyperactivity and behavioral sensitization following repeated injection in SHR, WKY and WIS (Cailhol and Mormede 1999, Frankowska, Nowak et al. 2009). MPH pretreatment (2.5 mg/kg/day i.p., for 10 days) administered outside the home cage during adolescence or early adulthood was reported to increase cocaine cross-sensitization evaluated 10 days after MPH in SHR compared to WKY and outbred Sprague-Dawley rats (Yetnikoff and Arvanitogiannis 2013). In contrast, home-cage administration of MPH (0.6 or 2.5 mg/kg/day i.p. for 6 days) did not alter sensitization to MPH in adolescent or adult SHR (Yang, Swann et al. 2006, Yang, Cuellar et al. 2011). The current study extends previous findings by employing a therapeutically relevant MPH dose and home-cage administration of MPH, and shows that treatment history did not alter cocaine sensitization during adulthood. Thus, independent of adolescent MPH treatment, SHR exhibited robust sensitization following repeated cocaine compared to control strains, revealing a strain-dependent vulnerability.

One explanation for these results may be differences in baseline locomotor activities between strains. For total number of horizontal beam breaks at baseline, SHR are hyperactive compared to WKY, but SHR are not different from WIS (Fig. 4A). As such, the baseline is higher in SHR and WIS, relative to WKY overall. If the effects of cocaine were dependent on the baseline rate, one would expect that WIS should react the same way as SHR, but this was not the case. Thus, the response to cocaine was not dependent on baseline. However, investigation of the behavior as repeated beam breaks of the same beam, interpreted as stereotypic behavior, provides a somewhat different perspective. Strain differences in stereotypic behavior were found with SHR > WKY and WIS (Fig. 4C). As such, one caveat is that the current study does not address whether in the absence of repeated cocaine injection, continued exposure to the open-field apparatus alters horizontal beam breaks activity differently in SHR compared to controls strains, and between MPH and vehicle treatment histories. In this regard, temporal changes in horizontal activity observed during a single session (Fig 4B) shows that strain differences in hyperactivity dissipated over prolonged exposure. Similar effects are expected with repeated exposure to an open-field chamber over days. Recently, strain differences in sensitization following 10 repeated MPH or saline injections revealed that locomotor activity for saline-treated SHR and WKY were not different (Yetnikoff and Arvanitogiannis 2013). Nonetheless, locomotor hyperactivity at baseline was not different between SHR and WIS, yet cocaine sensitization was greater in SHR, indicating that differences in behavior in cocaine-treated animals is not likely due to differences in baseline activity.

Expression of sensitization depends on increased glutamatergic transmission (Pierce, Bell et al. 1996, Perez, Gabach et al. 2010), increased DAT function and reduced D2 function (Mandt and Zahniser 2010, Merritt and Bachtell 2013) in striatum. SHR are less sensitive to glutamate-stimulated striatal DA and acetylcholine release, exhibit greater striatal DAT function and reduced D2 function compared to WKY and outbred rats (Tsuda, Tsuda et al. 1996, Fujita, Okutsu et al. 2003, Russell 2003, Miller, Pomerleau et al. 2012). These results suggest that the deficient striatal glutamatergic and DA function in SHR underlies the enhanced induction of cocaine sensitization. The lack of effect of adolescent treatment with MPH (1.5 mg/kg, p.o.) on cocaine sensitization may be partly due to the lack of effect of this dose on striatal DAT function (Somkuwar, Darna et al. 2013). This finding in SHR is complementary to clinical studies on ADHD showing no evidence for cocaine sensitization in adolescents and young adults that had been treated with MPH in childhood (Humphreys, Eng et al. 2013).

The current study highlights the persistence of some of the beneficial effects of adolescent MPH treatment with respect to decreased hyperactivity (both horizontal activity and stereotypy) during adulthood. These preclinical results align with the observed beneficial effects of stimulant treatment following early recognition and favorable long-term outcome in adult ADHD patients (Fredricksen, Halmoy et al, 2013). However, clinical studies suggest that initiation of MPH treatment during late childhood or early adolescence may increase the risk of substance use disorder in adulthood (Mannuzza, Klein et al. 2008, Dalsgaard, Mortensen et al. 2014), which is not an outcome associated with MPH treatment initiated earlier in childhood (Humphreys, Eng et al. 2013, Molina, Hinshaw et al. 2013). Conclusions from these clinical studies, that an increase in SUD risk that occurs when MPH

treatment begins in late childhood/early adolescence, also are consistent with other preclinical work showing that SHR treated with MPH during adolescence increases cocaine self-administration in adulthood even if treatment is discontinued after adolescence (Harvey, Sen et al. 2011, Baskin, Dwoskin et al. 2015).

Cocaine abuse vulnerability is linked to increased response inhibition deficits (Fillmore and Rush 2002, Li, Milivojevic et al. 2006). Response inhibition deficits are suggested to underlie the greater cocaine abuse liability in ADHD as well (Everitt, Belin et al. 2008, Groman, James et al. 2009, Winstanley, Olausson et al. 2010). Individuals with comorbid ADHD and cocaine dependence exhibit greater response inhibition deficits compared to those with ADHD without cocaine dependence, and compared to control (Crunelle, Veltman et al. 2013). Thus, the enhanced cocaine abuse vulnerability we previously observed in adult SHR receiving adolescent MPH treatment (Harvey, Sen et al. 2011, Baskin, Dwoskin et al. 2015) may be mediated, in part, by the reductions in response inhibition capacity observed herein. Although the role of previous medication status on response inhibition capacity in adults with ADHD has not been evaluated comprehensively, the current results in SHR suggest that adolescent MPH treatment may increase aspects of impulsivity in adults after adolescent MPH is discontinued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by grant R01 DA011716, P50 DA05312 and a Kentucky Opportunity Fellowship. The content is solely the responsibility of the authors and does not represent the official views of the National Institute on Drug Abuse. Experiments adhered to the Institutional Animal Care and Use Committee guidelines for animal research. We thank Emily Denehy and Travis McCuddy for technical assistance with data collection and Dr. Richard Charnigo and Dr. Federico Sanabria for assisting with data analyses.

References

Adriani W, Canese R, Podo F, Laviola G. 1H MRS-detectable metabolic brain changes and reduced impulsive behavior in adult rats exposed to methylphenidate during adolescence. Neurotoxicol Teratol. 2007; 29(1):116–125. [PubMed: 17196789]

Adriani W, Caprioli A, Granstrem O, Carli M, Laviola G. The spontaneously hypertensive-rat as an animal model of ADHD: evidence for impulsive and non-impulsive subpopulations. Neurosci Biobehav Rev. 2003; 27(7):639–651. [PubMed: 14624808]

Albrecht DS, Kareken DA, Christian BT, Dzemidzic M, Yoder KK. Cortical dopamine release during a behavioral response inhibition task. Synapse. 2014; 68(6):266–274. [PubMed: 24677429]

Almasy L, Blangero J. Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. American Journal of Medical Genetics. 2001; 105(1):42–44. [PubMed: 11424994]

Alsop B. Reprint of “Problems with spontaneously hypertensive rats (SHR) as a model of attention-deficit/hyperactivity disorder (AD/HD)”. J Neurosci Methods. 2007; 166(2):XV–XXI. [PubMed: 17980764]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Assoc; 2013.

Anastasio NC, Stoffel EC, Fox RG, Bubar MJ, Rice KC, Moeller FG, Cunningham KA. Serotonin (5-hydroxytryptamine) 5-HT(2A) receptor: association with inherent and cocaine-evoked behavioral disinhibition in rats. Behav Pharmacol. 2011; 22(3):248–261. [PubMed: 21499079]

Antonelli F, Ko JH, Miyasaki J, Lang AE, Houle S, Valzania F, Ray NJ, Strafella AP. Dopamine-agonists and impulsivity in Parkinson's disease: Impulsive choices vs. impulsive actions. Hum Brain Mapp. 2013

Aron AR. The neural basis of inhibition in cognitive control. The Neuroscientist: a review journal bringing neurobiology, neurology and psychiatry. 2007; 13(3):214–228.

Baayen RH, Davidson DJ, Bates DM. Mixed-effects modeling with crossed random effects for subjects and items. Journal of Memory and Language. 2008; 59(4):390–412.

Bari A, Mar AC, Theobald DE, Elands SA, Oganya KC, Eagle DM, Robbins TW. Prefrontal and monoaminergic contributions to stop-signal task performance in rats. J Neurosci. 2011; 31(25): 9254–9263. [PubMed: 21697375]

Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychological bulletin. 1997; 121(1):65–94. [PubMed: 9000892]

Baskin BM, Dwoskin LP, Kantak KM. Methylphenidate treatment beyond adolescence maintains increased cocaine self-administration in the spontaneously hypertensive rat model of attention deficit/hyperactivity disorder. Pharmacol Biochem Behav. 2015; 131:51–56. [PubMed: 25643872]

Bearden CE V, Reus I, Freimer NB. Why genetic investigation of psychiatric disorders is so difficult. Current Opinion in Genetics & Development. 2004; 14(3):280–286. [PubMed: 15172671]

Berridge CW, Devilbiss DM. Psychostimulants as cognitive enhancers: the prefrontal cortex, catecholamines, and attention-deficit/hyperactivity disorder. Biol Psychiatry. 2011; 69(12):e101–111. [PubMed: 20875636]

Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AF, Kelley AE, Schmeichel B, Hamilton C, Spencer RC. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol Psychiatry. 2006; 60(10): 1111–1120. [PubMed: 16806100]

Biederman J, Petty CR, Evans M, Small J, Faraone SV. How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatry research. 2010; 177(3):299–304. [PubMed: 20452063]

Brandon CL, Marinelli M, Baker LK, White FJ. Enhanced reactivity and vulnerability to cocaine following methylphenidate treatment in adolescent rats. Neuropsychopharmacology. 2001; 25(5): 651–661. [PubMed: 11682248]

Brenhouse HC, Sonntag KC, Andersen SL. Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. J Neurosci. 2008; 28(10):2375–2382. [PubMed: 18322084]

Bull E, Reavill C, Hagan JJ, Overend P, Jones DN. Evaluation of the spontaneously hypertensive rat as a model of attention deficit hyperactivity disorder: acquisition and performance of the DRL-60s test. Behavioural brain research. 2000; 109(1):27–35. [PubMed: 10699655]

Burton CL, Fletcher PJ. Age and sex differences in impulsive action in rats: the role of dopamine and glutamate. Behav Brain Res. 2012; 230(1):21–33. [PubMed: 22326372]

Cailhol S, Mormede P. Strain and sex differences in the locomotor response and behavioral sensitization to cocaine in hyperactive rats. Brain Res. 1999; 842(1):200–205. [PubMed: 10526110]

Carlezon WA Jr, Mague SD, Andersen SL. Enduring behavioral effects of early exposure to methylphenidate in rats. Biol Psychiatry. 2003; 54(12):1330–1337. [PubMed: 14675796]

Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. J Am Acad Child Adolesc Psychiatry. 2010; 49(12):1189–1201. quiz 1285. [PubMed: 21093769]

Castellanos FX, Sonuga-Barke EJ, Scheres A, Di Martino A, Hyde C, Walters JR. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol Psychiatry. 2005; 57(11):1416–1423. [PubMed: 15950016]

CDC. Centers for Disease Control and Prevention, National Health and Nutrition Examination Survey. 2007. http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm/

Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry. 2003; 160(6):1041–1052. [PubMed: 12777258]

Clark L, Blackwell AD, Aron AR, Turner DC, Dowson J, Robbins TW, Sahakian BJ. Association between response inhibition and working memory in adult ADHD: a link to right frontal cortex pathology? Biological Psychiatry. 2007; 61(12):1395–1401. [PubMed: 17046725]

Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naive boys with attention-deficit/hyperactivity disorder. Biological Psychiatry. 2007; 62(9): 954–962. [PubMed: 17543895]

Counotte DS, Smit AB, Pattij T, Spijker S. Development of the motivational system during adolescence, and its sensitivity to disruption by nicotine. Dev Cogn Neurosci. 2011; 1(4):430–443. [PubMed: 22436565]

Crosbie J, Perusse D, Barr CL, Schachar RJ. Validating psychiatric endophenotypes: Inhibitory control and attention deficit hyperactivity disorder. Neuroscience and Biobehavioral Reviews. 2008; 32(1):40–55. [PubMed: 17976721]

Crunelle CL, Veltman DJ, van Emmerik-van Oortmerssen K, Booij J, van den Brink W. Impulsivity in adult ADHD patients with and without cocaine dependence. Drug and Alcohol Dependence. 2013; 129(1–2):18–24. [PubMed: 23026814]

Dalley JW, Theobald DE, Eagle DM, Passetti F, Robbins TW. Deficits in impulse control associated with tonically-elevated serotonergic function in rat prefrontal cortex. Neuropsychopharmacology. 2002; 26(6):716–728. [PubMed: 12007742]

Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood - a naturalistic long-term follow-up study. Addict Behav. 2014; 39(1):325–328. [PubMed: 24090624]

De La Garza R 2nd, Mahoney JJ 3rd. A distinct neurochemical profile in WKY rats at baseline and in response to acute stress: implications for animal models of anxiety and depression. Brain Res. 2004; 1021(2):209–218. [PubMed: 15342269]

Doremus-Fitzwater TL, Varlinskaya EI, Spear LP. Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. Brain Cogn. 2010; 72(1):114–123. [PubMed: 19762139]

Evenden JL. Varieties of impulsivity. Psychopharmacology. 1999; 146(4):348–361. [PubMed: 10550486]

Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW. Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos Trans R Soc Lond B Biol Sci. 2008; 363(1507):3125–3135. [PubMed: 18640910]

Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med. 2006; 36(2):159–165. [PubMed: 16420712]

Ferguson SA, Paule MG, Cada A, Fogle CM, Gray EP, Berry KJ. Baseline behavior, but not sensitivity to stimulant drugs, differs among spontaneously hypertensive, Wistar-Kyoto, and Sprague-Dawley rat strains. Neurotoxicology and teratology. 2007; 29(5):547–561. [PubMed: 17689921]

Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend. 2002; 66(3):265–273. [PubMed: 12062461]

Frankowska M, Nowak E, Filip M. Effects of GABAB receptor agonists on cocaine hyperlocomotor and sensitizing effects in rats. Pharmacol Rep. 2009; 61(6):1042–1049. [PubMed: 20081239]

Fujita S, Okutsu H, Yamaguchi H, Nakamura S, Adachi K, Saigusa T, Koshikawa N. Altered pre- and postsynaptic dopamine receptor functions in spontaneously hypertensive rat: an animal model of attention-deficit hyperactivity disorder. J Oral Sci. 2003; 45(2):75–83. [PubMed: 12930130]

Fumagalli F, Cattaneo A, Caffino L, Ibba M, Racagni G, Carboni E, Gennarelli M, Riva MA. Sub-chronic exposure to atomoxetine up-regulates BDNF expression and signalling in the brain of adolescent spontaneously hypertensive rats: comparison with methylphenidate. Pharmacol Res. 2010; 62(6):523–529. [PubMed: 20691787]

Gerasimov MR, Franceschi M, Volkow ND, Gifford A, Gatley SJ, Marsteller D, Molina PE, Dewey SL. Comparison between intraperitoneal and oral methylphenidate administration: A microdialysis and locomotor activity study. J Pharmacol Exp Ther. 2000; 295(1):51–57. [PubMed: 10991960]

Goldman LS, Genel M, Bezman RJ, Slanetz PJ. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Council on Scientific Affairs, American Medical Association. JAMA. 1998; 279(14):1100–1107. [PubMed: 9546570]

Gottesman, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003; 160(4):636–645. [PubMed: 12668349]

Groman SM, James AS, Jentsch JD. Poor response inhibition: At the nexus between substance abuse and attention deficit/hyperactivity disorder. Neuroscience and Biobehavioral Reviews. 2009; 33(5):690–698. [PubMed: 18789354]

Hankosky ER, Gulley JM. Performance on an impulse control task is altered in adult rats exposed to amphetamine during adolescence. Dev Psychobiol. 2013; 55(7):733–744. [PubMed: 22778047]

Harvey RC, Jordan CJ, Tassin DH, Moody KR, Dwoskin LP, Kantak KM. Performance on a strategy set shifting task during adolescence in a genetic model of attention deficit/hyperactivity disorder: methylphenidate vs. atomoxetine treatments. Behav Brain Res. 2013; 244:38–47. [PubMed: 23376704]

Harvey RC, Sen S, Deaciuc A, Dwoskin LP, Kantak KM. Methylphenidate treatment in adolescent rats with an attention deficit/hyperactivity disorder phenotype: cocaine addiction vulnerability and dopamine transporter function. Neuropsychopharmacology. 2011; 36(4):837–847. [PubMed: 21150910]

Hill JC, Covarrubias P, Terry J, Sanabria F. The effect of methylphenidate and rearing environment on behavioral inhibition in adult male rats. Psychopharmacology. 2012; 219(2):353–362. [PubMed: 22057663]

Humphreys KL, Eng T, Lee SS. Stimulant Medication and Substance Use Outcomes A Meta-analysis. Jama Psychiatry. 2013; 70(7):740–749. [PubMed: 23754458]

Jastrzebska J, Frankowska M, Szumiec L, Sadakierska-Chudy A, Haduch A, Smaga I, Bystrowska B, Daniel WA, Filip M. Cocaine self-administration in Wistar-Kyoto rats: a behavioral and biochemical analysis. Behav Brain Res. 2015; 293:62–73. [PubMed: 26192911]

Kantak KM, Singh T, Kerstetter KA, Dembro KA, Mutebi MM, Harvey RC, Deschepper CF, Dwoskin LP. Advancing the spontaneous hypertensive rat model of attention deficit/hyperactivity disorder. Behav Neurosci. 2008; 122(2):340–357. [PubMed: 18410173]

Kuczenski R, Segal DS. Exposure of adolescent rats to oral methylphenidate: preferential effects on extracellular norepinephrine and absence of sensitization and cross-sensitization to methamphetamine. J Neurosci. 2002; 22(16):7264–7271. [PubMed: 12177221]

Langen B, Dost R. Comparison of SHR, WKY and Wistar rats in different behavioural animal models: effect of dopamine D1 and alpha2 agonists. Atten Defic Hyperact Disord. 2011; 3(1):1–12. [PubMed: 21432613]

Li CS, Milivojevic V, Kemp K, Hong K, Sinha R. Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. Drug Alcohol Depend. 2006; 85(3):205–212. [PubMed: 16725282]

Mandt BH, Zahniser NR. Low and high cocaine locomotor responding male Sprague-Dawley rats differ in rapid cocaine-induced regulation of striatal dopamine transporter function. Neuropharmacology. 2010; 58(3):605–612. [PubMed: 19951714]

Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult psychiatric status of hyperactive boys grown up. Am J Psychiatry. 1998; 155(4):493–498. [PubMed: 9545994]

Mannuzza S, Klein RG, Truong NL, Moulton JL 3rd, Roizen ER, Howell KH, Castellanos FX. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry. 2008; 165(5):604–609. [PubMed: 18381904]

Martins S, Tramontina S, Polanczyk G, Eizirik M, Swanson JM, Rohde LA. Weekend holidays during methylphenidate use in ADHD children: a randomized clinical trial. J Child Adolesc Psychopharmacol. 2004; 14(2):195–206. [PubMed: 15319017]

McCarthy S, Asherson P, Coghill D, Hollis C, Murray M, Potts L, Sayal K, de Soysa R, Taylor E, Williams T, Wong IC. Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. Br J Psychiatry. 2009; 194(3):273–277. [PubMed: 19252159]

McClure GY, McMillan DE. Effects of drugs on response duration differentiation. VI: differential effects under differential reinforcement of low rates of responding schedules. The Journal of pharmacology and experimental therapeutics. 1997; 281(3):1368–1380. [PubMed: 9190873]

Merritt KE, Bachtell RK. Initial d2 dopamine receptor sensitivity predicts cocaine sensitivity and reward in rats. PLoS One. 2013; 8(11):e78258. [PubMed: 24223783]

Mika A, Mazur GJ, Hoffman AN, Talboom JS, Bimonte-Nelson HA, Sanabria F, Conrad CD. Chronic stress impairs prefrontal cortex-dependent response inhibition and spatial working memory. Behavioral neuroscience. 2012; 126(5):605–619. [PubMed: 22905921]

Mill J, Sagvolden T, Asherson P. Sequence analysis of Drd2, Drd4, and Dat1 in SHR and WKY rat strains. Behav Brain Funct. 2005; 1:24. [PubMed: 16356184]

Miller EM, Pomerleau F, Huettl P, Russell VA, Gerhardt GA, Glaser PE. The spontaneously hypertensive and Wistar Kyoto rat models of ADHD exhibit sub-regional differences in dopamine release and uptake in the striatum and nucleus accumbens. Neuropharmacology. 2012; 63(8): 1327–1334. [PubMed: 22960443]

Molina BS, Hinshaw SP, Eugene Arnold L, Swanson JM, Pelham WE, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff HB, Greenhill LL, Jensen PS, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S. M. T. A. C. Group. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry. 2013; 52(3):250–263. [PubMed: 23452682]

Monterosso J, Ainslie G. Beyond discounting: possible experimental models of impulse control. Psychopharmacology (Berl). 1999; 146(4):339–347. [PubMed: 10550485]

Moron JA, Brockington A, Wise RA, Rocha BA, Hope BT. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci. 2002; 22(2):389–395. [PubMed: 11784783]

Orduna V, Valencia-Torres L, Bouzas A. DRL performance of spontaneously hypertensive rats: dissociation of timing and inhibition of responses. Behavioural brain research. 2009; 201(1):158–165. [PubMed: 19428629]

Pardey MC, Kumar NN, Goodchild AK, Cornish JL. Catecholamine receptors differentially mediate impulsive choice in the medial prefrontal and orbitofrontal cortex. J Psychopharmacol. 2013; 27(2):203–212. [PubMed: 23135240]

Pare WP, Kluczynski J. Differences in the stress response of Wistar-Kyoto (WKY) rats from different vendors. Physiol Behav. 1997; 62(3):643–648. [PubMed: 9272677]

Pattij T, Broersen LM, van der Linde J, Groenink L, van der Gugten J, Maes RA, Olivier B. Operant learning and differential-reinforcement-of-low-rate 36-s responding in 5-HT1A and 5-HT1B receptor knockout mice. Behav Brain Res. 2003; 141(2):137–145. [PubMed: 12742250]

Pattij T, Vanderschuren LJ. The neuropharmacology of impulsive behaviour. Trends Pharmacol Sci. 2008; 29(4):192–199. [PubMed: 18304658]

Perez MF, Gabach LA, Almiron RS, Carlini VP, De Barioglio SR, Ramirez OA. Different chronic cocaine administration protocols induce changes on dentate gyrus plasticity and hippocampal dependent behavior. Synapse. 2010; 64(10):742–753. [PubMed: 20698030]

Peterson JD, Wolf ME, White FJ. Impaired DRL 30 performance during amphetamine withdrawal. Behav Brain Res. 2003; 143(1):101–108. [PubMed: 12842301]

Pierce RC, Bell K, Duffy P, Kalivas PW. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. J Neurosci. 1996; 16(4):1550–1560. [PubMed: 8778304]

Rhodes SM, Coghill DR, Matthews K. Acute neuropsychological effects of methylphenidate in stimulant drug-naive boys with ADHD II--broader executive and non-executive domains. Journal of child psychology and psychiatry, and allied disciplines. 2006; 47(11):1184–1194.

Richards JB, Sabol KE, Seiden LS. DRL interresponse-time distributions: quantification by peak deviation analysis. Journal of the experimental analysis of behavior. 1993; 60(2):361–385. [PubMed: 8409824]

Robison LM, Sclar DA, Skaer TL, Galin RS. National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990–1995. Clin Pediatr (Phila). 1999; 38(4):209–217. [PubMed: 10326176]

Roessner V, Manzke T, Becker A, Rothenberger A, Bock N. Development of 5-HT transporter density and long-term effects of methylphenidate in an animal model of ADHD. World J Biol Psychiatry. 2009; 10(4 Pt 2):581–585. [PubMed: 19172439]

Rothmond DA, Weickert CS, Webster MJ. Developmental changes in human dopamine neurotransmission: cortical receptors and terminators. BMC Neurosci. 2012; 13:18. [PubMed: 22336227]

Russell V, de Villiers A, Sagvolden T, Lamm M, Taljaard J. Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention-deficit hyperactivity disorder--the spontaneously hypertensive rat. Brain Res. 1995; 676(2):343–351. [PubMed: 7614004]

Russell VA. In vitro glutamate-stimulated release of dopamine from nucleus accumbens core and shell of spontaneously hypertensive rats. Metab Brain Dis. 2003; 18(2):161–168. [PubMed: 12822835]

Sagvolden T, Aase H, Zeiner P, Berger D. Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder. Behavioural brain research. 1998; 94(1):61–71. [PubMed: 9708840]

Sagvolden T, Dasbanerjee T, Zhang-James Y, Middleton F, Faraone S. Behavioral and genetic evidence for a novel animal model of Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive Subtype. Behavioral and brain functions: BBF. 2008; 4:56. [PubMed: 19046438]

Sagvolden T, Johansen EB, Woien G, Walaas SI, Storm-Mathisen J, Bergersen LH, Hvalby O, Jensen V, Aase H, Russell VA, Killeen PR, Dasbanerjee T, Middleton FA, Faraone SV. The spontaneously hypertensive rat model of ADHD--the importance of selecting the appropriate reference strain. Neuropharmacology. 2009; 57(7–8):619–626. [PubMed: 19698722]

Sagvolden T V, Russell A, Aase H, Johansen EB, Farshbaf M. Rodent models of attention-deficit/hyperactivity disorder. Biological Psychiatry. 2005; 57(11):1239–1247. [PubMed: 15949994]

Sagvolden T V, Russell A, Aase H, Johansen EB, Farshbaf M. Rodent models of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57(11):1239–1247. [PubMed: 15949994]

Sanabria F, Killeen PR. Evidence for impulsivity in the Spontaneously Hypertensive Rat drawn from complementary response-withholding tasks. Behavioral and brain functions: BBF. 2008; 4:7. [PubMed: 18261220]

Schenk S, Horger BA, Peltier R, Shelton K. Supersensitivity to the reinforcing effects of cocaine following 6-hydroxydopamine lesions to the medial prefrontal cortex in rats. Brain research. 1991; 543(2):227–235. [PubMed: 1905576]

Schlicker E, Classen K, Gothert M. Presynaptic serotonin receptors and alpha-adrenoceptors on central serotoninergic and noradrenergic neurons of normotensive and spontaneously hypertensive rats. J Cardiovasc Pharmacol. 1988; 11(5):518–528. [PubMed: 2455837]

Simon NW, Beas BS, Montgomery KS, Haberman RP, Bizon JL, Setlow B. Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. Eur J Neurosci. 2013; 37(11):1779–1788. [PubMed: 23510331]

Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, van der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. Journal of the American Academy of Child and Adolescent Psychiatry. 2003; 42(10):1242–1248. [PubMed: 14560175]

Sokolowski JD, Salamone JD. Effects of dopamine depletions in the medial prefrontal cortex on DRL performance and motor activity in the rat. Brain research. 1994; 642(1–2):20–28. [PubMed: 8032881]

Somkuwar SS, Darna M, Kantak KM, Dwoskin LP. Adolescence methylphenidate treatment in a rodent model of attention deficit/hyperactivity disorder: dopamine transporter function and cellular distribution in adulthood. Biochem Pharmacol. 2013; 86(2):309–316. [PubMed: 23623751]

Somkuwar SS, Kantak KM, Dwoskin LP. Effect of methylphenidate treatment during adolescence on norepinephrine transporter function in orbitofrontal cortex in a rat model of attention deficit hyperactivity disorder. J Neurosci Methods. 2015; 252:55–63. [PubMed: 25680322]

Spear L. Modeling adolescent development and alcohol use in animals. Alcohol Res Health. 2000; 24(2):115–123. [PubMed: 11199278]

Stein N, Landis R. Differential reinforcement of low rates performance by impulsive and reflective children. Journal of experimental child psychology. 1975; 19(1):37–50. [PubMed: 1117254]

Thanos PK, Michaelides M, Benveniste H, Wang GJ, Volkow ND. Effects of chronic oral methylphenidate on cocaine self-administration and striatal dopamine D2 receptors in rodents. Pharmacology, biochemistry, and behavior. 2007; 87(4):426–433.

Tsuda K, Tsuda S, Goldstein M, Nishio I, Masuyama Y. Glutamatergic regulation of [3H]acetylcholine release in striatal slices of normotensive and spontaneously hypertensive rats. Neurochem Int. 1996; 29(3):231–237. [PubMed: 8885281]

Umehara M, Ago Y, Fujita K, Hiramatsu N, Takuma K, Matsuda T. Effects of serotonin-norepinephrine reuptake inhibitors on locomotion and prefrontal monoamine release in spontaneously hypertensive rats. Eur J Pharmacol. 2013; 702(1–3):250–257. [PubMed: 23376565]

Umehara M, Ago Y, Kawanai T, Fujita K, Hiramatsu N, Takuma K, Matsuda T. Methylphenidate and venlafaxine attenuate locomotion in spontaneously hypertensive rats, an animal model of attention-deficit/hyperactivity disorder, through alpha2-adrenoceptor activation. Behav Pharmacol. 2013; 24(4):328–331. [PubMed: 23751518]

Urban KR, Li YC, Gao WJ. Treatment with a clinically-relevant dose of methylphenidate alters NMDA receptor composition and synaptic plasticity in the juvenile rat prefrontal cortex. Neurobiol Learn Mem. 2013; 101:65–74. [PubMed: 23333502]

Urban KR, Waterhouse BD, Gao WJ. Distinct age-dependent effects of methylphenidate on developing and adult prefrontal neurons. Biol Psychiatry. 2012; 72(10):880–888. [PubMed: 22609367]

van den Bergh FS, Bloemarts E, Chan JS, Groenink L, Olivier B, Oosting RS. Spontaneously hypertensive rats do not predict symptoms of attention-deficit hyperactivity disorder. Pharmacology, biochemistry, and behavior. 2006; 83(3):380–390.

Vendruscolo LF, Izidio GS, Takahashi RN, Ramos A. Chronic methylphenidate treatment during adolescence increases anxiety-related behaviors and ethanol drinking in adult spontaneously hypertensive rats. Behav Pharmacol. 2008; 19(1):21–27. [PubMed: 18195591]

Verbeke, G.; Molenberghs, G. Springer series in statistics. New York: Springer; 2000. Linear mixed models for longitudinal data; p. xxiip. 5681 online resource

Wainwright PE, Leatherdale ST, Dubin JA. Advantages of mixed effects models over traditional ANOVA models in developmental studies: a worked example in a mouse model of fetal alcohol syndrome. Dev Psychobiol. 2007; 49(7):664–674. [PubMed: 17943976]

Wargin W, Patrick K, Kilts C, Gualtieri CT, Ellington K, Mueller RA, Kraemer G, Breese GR. Pharmacokinetics of methylphenidate in man, rat and monkey. The Journal of pharmacology and experimental therapeutics. 1983; 226(2):382–386. [PubMed: 6410043]

Winstanley CA, Olausson P, Taylor JR, Jentsch JD. Insight into the relationship between impulsivity and substance abuse from studies using animal models. Alcoholism, clinical and experimental research. 2010; 34(8):1306–1318.

Yang PB, Cuellar DO 3rd, Swann AC, Dafny N. Age and genetic strain differences in response to chronic methylphenidate administration. Behav Brain Res. 2011; 218(1):206–217. [PubMed: 21111006]

Yang PB, Swann AC, Dafny N. Acute and chronic methylphenidate dose-response assessment on three adolescent male rat strains. Brain Res Bull. 2006; 71(1–3):301–310. [PubMed: 17113960]

Yetnikoff L, Arvanitogiannis A. Differential sensitivity to the acute and sensitizing behavioral effects of methylphenidate as a function of strain in adolescent and young adult rats. Behav Brain Funct. 2013; 9:38. [PubMed: 24134881]

Yetnikoff L, Arvanitogiannis A. Differential sensitivity to the acute and sensitizing behavioral effects of methylphenidate as a function of strain in adolescent and young adult rats. Behav Brain Funct. 2013; 9(1):38. [PubMed: 24134881]

Zhang-James Y, Middleton FA, Faraone SV. Genetic architecture of Wistar-Kyoto rat and spontaneously hypertensive rat substrains from different sources. Physiol Genomics. 2013; 45(13):528–538. [PubMed: 23673728]

Highlights

- Lasting effects of discontinued adolescent methylphenidate treatment are reported
- Treatment decreased hyperactivity in adulthood in SHR, a model of ADHD
- Treatment discontinuation increased impulsivity in adult SHR compared to vehicle
- Treatment discontinuation had no effects on cocaine sensitivity in SHR or control
- SHR show greater impulsivity, hyperactivity and cocaine sensitization than controls

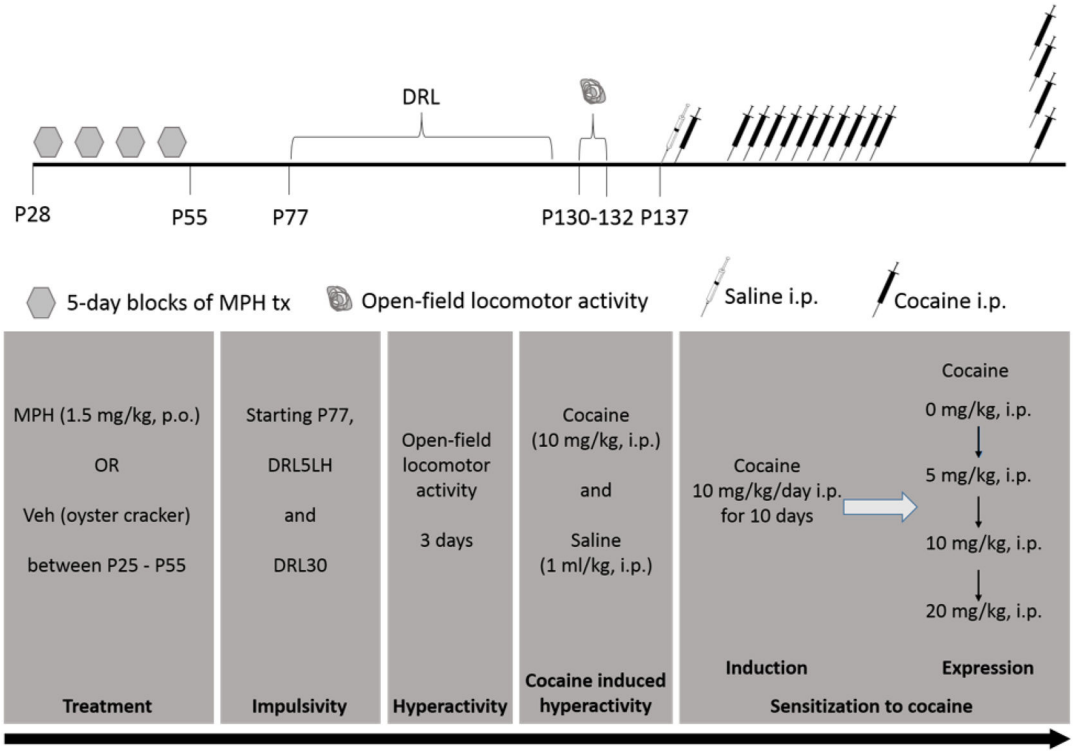

Fig 1.
Schematic of treatments and conduct of experiments.

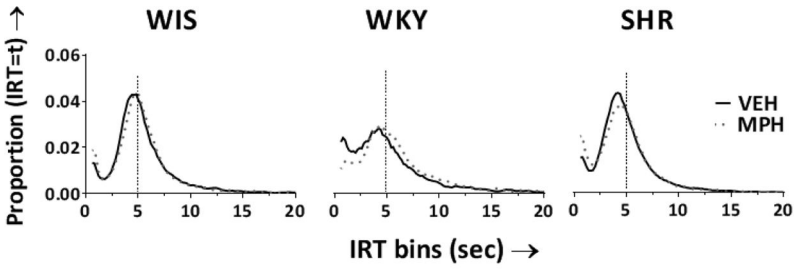

Fig 2.

Under DRL5LH, discontinuation of chronic methylphenidate (MPH) treatment following adolescence did not alter response inhibition capacity in adult SHR. Mean inter-response time (IRT) distributions were not different between MPH (dotted curves) and vehicle (VEH, solid curves) groups, except for WKY (middle panel). Mean IRT distributions are presented as 1-s moving averages of IRTs for SHR, WKY and WIS under DRL5LH. n = 5–6/group.

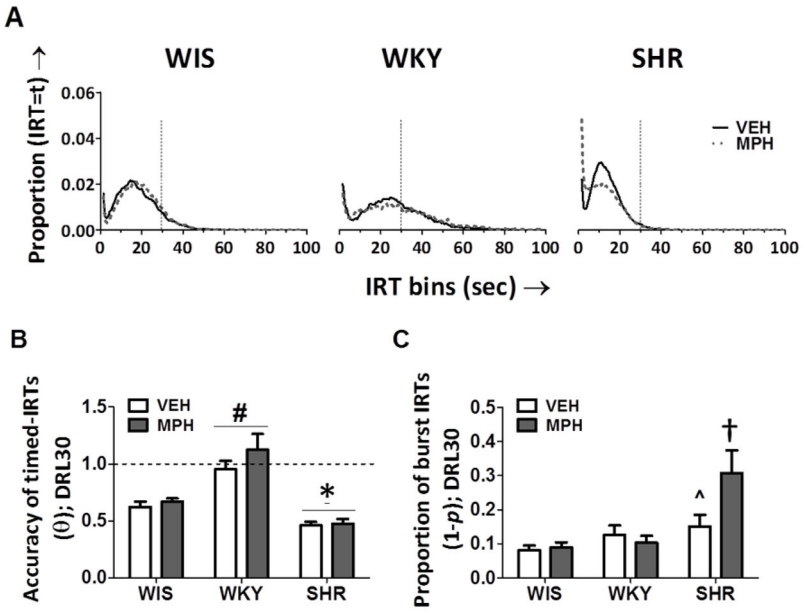

Fig 3.

Under DRL30, discontinuation of chronic methylphenidate (MPH) treatment following adolescence increased the response inhibition deficit in adult SHR. (A) In adult SHR (right panel), but not in control strains, discontinuation of adolescent treatment with MPH (dotted curves) altered inter-response time (IRT) distribution by increasing burst IRTs and proportionately decreasing timed IRTs. (B) Compared to WKY and WIS rats, adult SHR under the DRL30 schedule exhibited reduced accuracy of timed IRTs (mean ± S.E.M.) irrespective of adolescent treatment with MPH (gray bars) or vehicle (VEH, white bars). Also, accuracy of timed IRTs was reduced in WIS compared to WKY. (C) Compared to WKY and WIS, adult SHR administered VEH during adolescence emitted a greater proportion of burst IRTs (mean ± S.E.M.). MPH treatment during adolescence further increased burst IRTs during adulthood. Mean IRT distributions are presented as 5-s moving averages of IRTs for SHR, WKY and WIS under DRL30. n = 5–6/group; † $p \leq 0.05$ compared to the respective VEH control and MPH-treated WKY and WIS; ^ $p \leq 0.05$ compared to VEH-treated WKY and WIS; * $p \leq 0.05$ main effect of strain, different from WKY and WIS; $^{\#}$ $p \leq 0.05$ main effect of strain, different from WIS.

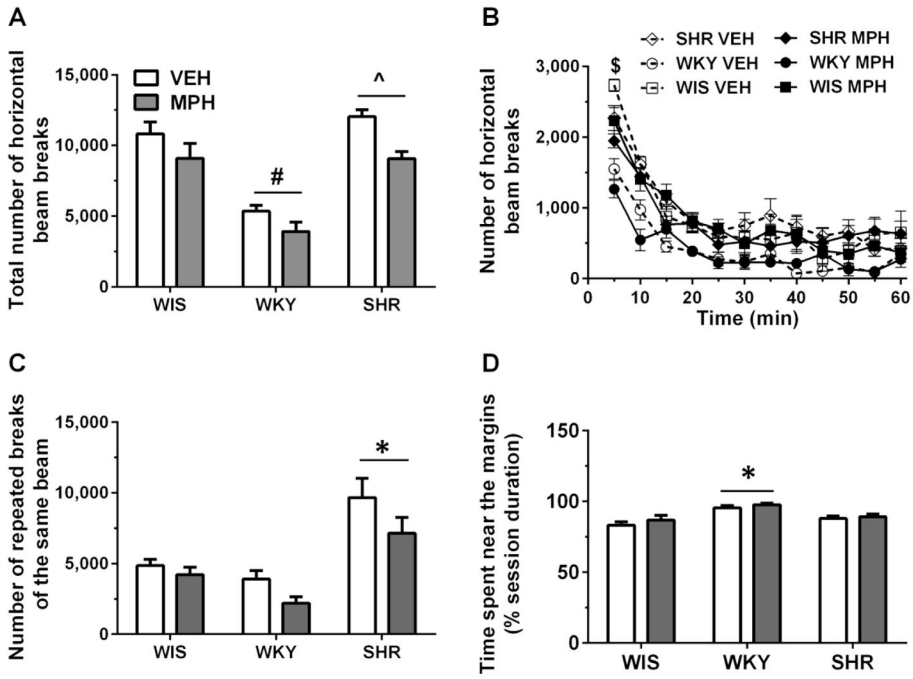

Fig 4.

Discontinuation of chronic methylphenidate (MPH, grey bars) treatment following adolescence decreased hyperactivity in adult SHR. (A) SHR exhibited greater total horizontal beam breaks (mean ± S.E.M.) compared to WKY, while that by adult WKY was fewer compared to WIS rats. (B) Adult SHR that received MPH during adolescence (closed diamonds), but not SHR administered vehicle (VEH; open diamonds) during adolescence, showed reduced horizontal beam breaks during the first 5-min bin compared to adult WIS rats that received VEH during adolescence (open squares). (C) SHR exhibited greater repeated breaks of the same beam in open-field chambers compared to WKY and WIS rats. (D) Time spent near the margins was increased in WKY compared to both WIS and SHR. Finally, discontinuation of adolescent treatment with MPH (gray bars) decreased both total number of beam breaks (A) and repeated breaks of the same beam (C) in adult rats compared to vehicle control (VEH, white bars). n = 5–6/group; * $p \leq 0.05$ compared to all other strains; $^{\#}$ $p \leq 0.05$ compared to WIS; $^{\wedge}$ $p \leq 0.05$ compared to WKY; $^{\$}$ $p \leq 0.05$ compared to WIS-VEH.

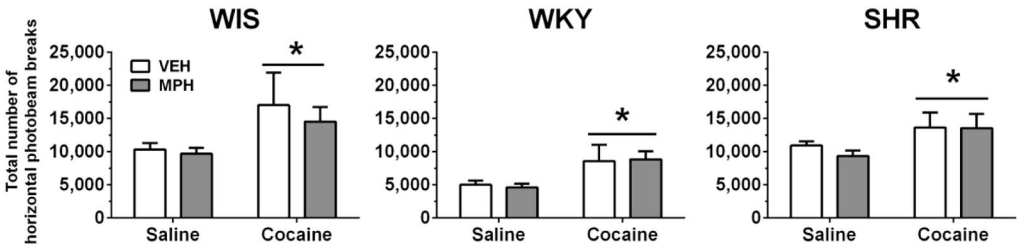

Fig 5.

Acute cocaine injection induced hyperactivity in adult WIS, WKY rats and SHR compared to saline injection. Discontinuation of methylphenidate (MPH; gray bars) and vehicle (VEH; white bars) treatments did not alter cocaine-induced hyperactivity in WIS, WKY and SHR. Values are mean ± S.E.M. for number of horizontal photobeam breaks. Saline data reflects locomotor activity for 1 hour following the injection on the day after habituation. n = 5–6/group; *$p<0.05$ main effect of cocaine, compared to respective saline control.

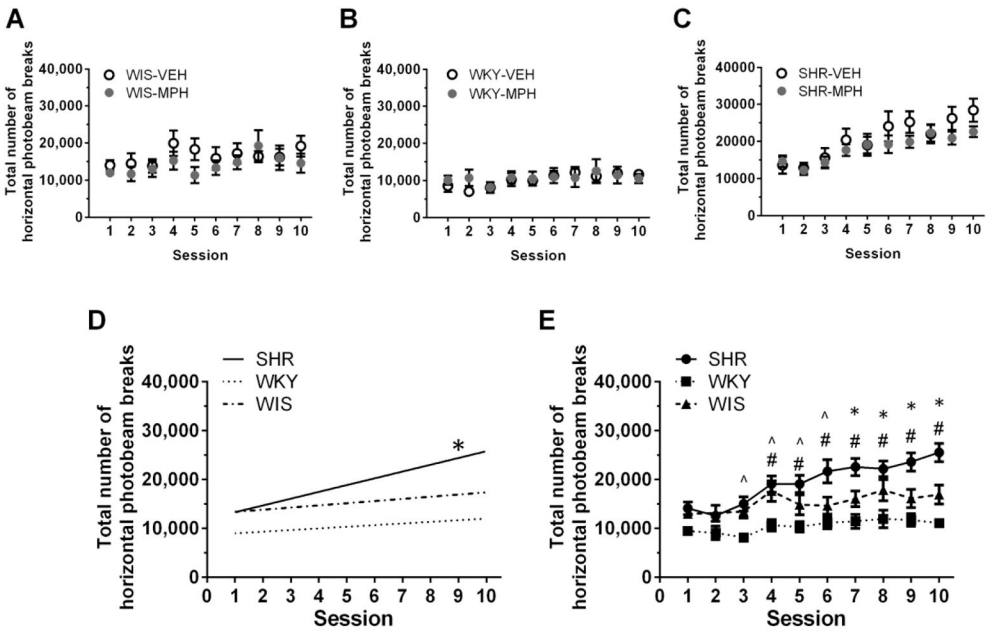

Fig 6.

Repeated cocaine (10 mg/kg, i.p.) injection induced sensitization in adult SHR, but not in adult WIS or WKY rats. Discontinuation of methylphenidate (MPH; white symbols) and vehicle (VEH; gray symbols) treatments did not alter cocaine-induced hyperactivity in WIS, WKY and SHR. Values are mean ± S.E.M. for number of horizontal photobeam breaks following cocaine injections for sessions 1–10. n = 5–6/group (A–C). Linear regressions (D) and observed data (E) for induction of sensitization for cocaine for individual strains (collapsed across VEH and MPH groups) are presented. n = 11–12/strain; *$p<0.05$ compared to WKY and WIS, ^$p<0.05$ compared to WKY, $^{\#}p<0.05$ compared to 1^{st} session of SHR.

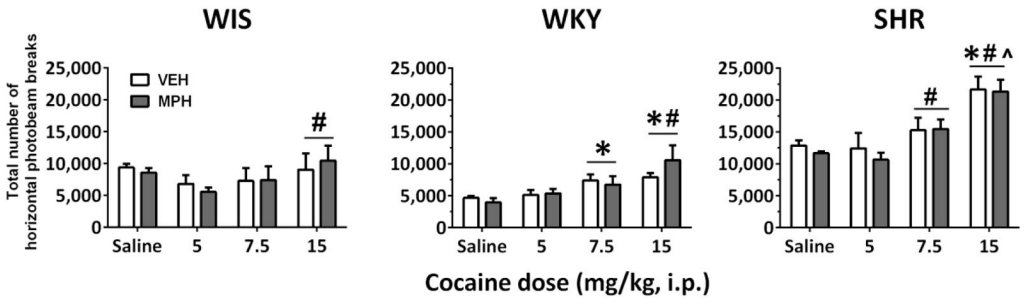

Fig 7.

Cocaine (5–15 mg/kg, i.p.) dose-dependently increased hyperactivity in adult WIS, WKY rats and SHR compared to saline injection. Discontinuation of methylphenidate (MPH; gray bars) and vehicle (VEH; white bars) treatments did not alter expression of cocaine-sensitization in WIS, WKY and SHR. Cocaine sensitivity was greater in SHR compared to both WKY and WIS, at all doses except saline at which activity was greater in SHR and WIS compared to WKY. Values are mean ± S.E.M. for number of horizontal photobeam breaks. Saline data reflects locomotor activity for 30 min following 14 days of no cocaine administration after the induction of cocaine sensitization. n = 5–6/group; * $p<0.05$ compared to saline; # $p<0.05$ compared to 5 mg/kg cocaine; ^ $p<0.05$ compared to 7.5 mg/kg cocaine.

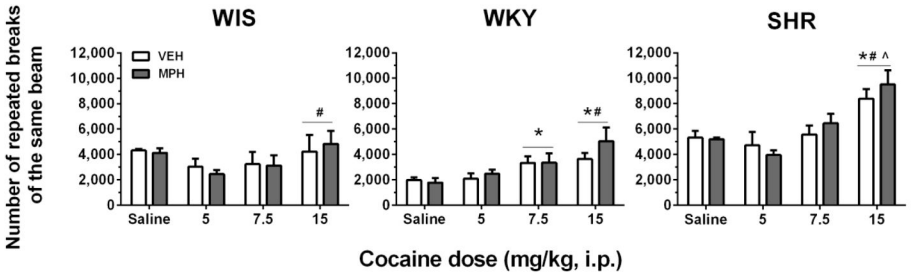

Fig 8.

Cocaine (5–15 mg/kg, i.p.) dose-dependently increased hyperactivity in adult WIS, WKY rats and SHR compared to saline injection. Discontinuation of methylphenidate (MPH; gray bars) and vehicle (VEH; white bars) treatments did not alter expression of cocaine-sensitization in WIS, WKY and SHR. Repeated breaks of the same beam were greater in SHR than WKY at all doses and greater than WIS at the two highest cocaine doses only. Values are mean ± S.E.M. for number of horizontal photobeam breaks. Saline data reflects locomotor activity for 30 min following 14 days of no cocaine administration after the induction of cocaine sensitization. n = 5–6/group; * $p<0.05$ compared to saline; $^{\#}$ $p<0.05$ compared to 5 mg/kg cocaine; ^ $p<0.05$ compared to 7.5 mg/kg cocaine.

Table 1

SHR exhibited reduced efficiency (% responses reinforced) compared to controls, but chronic methylphenidate (MPH) treatment during adolescence or adulthood did not alter efficiency in adult SHR, WKY and WIS rats under DRL5LH and DRL30 schedules.

		Efficiency under DRL5LH		Efficiency under DRL30	
		VEH	MPH	VEH	MPH
Experiment 1 Adolescent Treatments	SHR	23.2 ± 1.00 [a]	22.6 ± 0.92	2.52 ± 0.83	2.81 ± 0.92
	WKY	25.7 ± 1.56	29.7 ± 1.59	33.8 ± 6.86	41.6 ± 7.60
	WIS	27.1 ± 1.06	28.0 ± 0.96	10.8 ± 2.86	12.4 ± 2.43
	F_{strain}	F[2,29] = 10.5; p < 0.05 SHR < WIS = WKY		F[2,29] = 32.9; p < 0.05 SHR < WIS < WKY	

[a] Values are mean ± S.E.M.; n = 6/group, except WKY-VEH for Experiment 1, n = 5/group.